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Pancreatoblastoma: Case Report and Review of Treatment in the Literature

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A case of pancreatoblastoma arising from the body-to-tail of the pancreas in a 5-year-old boy is presented. The patient underwent exploratory laparotomy and, 11 days later, resection of the tumor (partial pancreatectomy, pyloroplasty, and splenectomy). Before resection, cyclophosphamide and vincristine were administered. Because of tumor spillage during resection, a combination of chemotherapy (administration of cyclophosphamide and adriamycin on that day) and postoperative radiotherapy was given. Nine months after resection, partial hepatectomy was performed for liver metastasis and consolidated by a more intensive chemotherapy regimen using cisplatin, adriamycin, vincristine, and cyclophosphamide. After completion of the chemotherapy, the patient had a 14-month uneventful course, and a locally recurrent tumor was treated by the fourth surgery (extirpation of the recurrent tumor, partial hepatectomy, partial colectomy, and partial gastrectomy) and intraoperative radiation. Thereafter, the boy has shown no evidence of disease at 3 years 8 months. The literature of pancreatoblastoma is reviewed from the therapeutic viewpoint.

Key words: pancreatoblastoma, alpha-fetoprotein, resection, chemotherapy, radiotherapy

INTRODUCTION

Pancreatoblastoma, a neoplasm of the pancreas, is rare in childhood and extremely rare in adulthood [1–3]. Histologically, monomorphic epithelial cells forming solid, trabecular, and acinar structures are admixed with squamoid corpuscles [4]. The tumor, at least partially encapsulated, arises from any region of the pancreas. Prognosis after complete removal of the tumor appears to be favorable, but in some cases tumor spillage during resection is inevitable. Moreover, the tumor is often unresectable at diagnosis.

We present here a case of pancreatoblastoma in a boy in whom liver metastasis and subsequently local recurrence took place after tumor resection in spite of the consolidation therapy, but there has been no evidence of disease 3 years and 8 months after the fourth surgery consolidated by intraoperative radiation (20 Gy). We also review the literature from the therapeutic point of view.

CASE REPORT

A 5-year-old boy was admitted on June 9, 1989, because of abdominal protuberance noticed by chance by an aunt. He complained of neither abdominal pain, vomiting, diarrhea, constipation, appetite loss, nor fever. On physical examination, there was a firm, immobile, slightly tender tumor in the upper abdomen, extending up to 17 cm below the xyphoid process. He showed neither hepatosplenomegaly nor lymph node swelling. Laboratory examination showed elevation of the serum levels of tissue polypeptide antigen (870 U/l; normal < 110 U/l), alpha-fetoprotein (531 ng/ml; normal < 5 ng/ml), neuron specific enolase (45.6 ng/ml; normal < 10 ng/ml), trypsin (> 1,100 ng/ml; normal 110–460 ng/ml), lipase (146 U; normal 0–70 U), and lactate dehydrogenase (784 U; normal 130–240 U). The serum levels of amylase, carcinoembryonic antigen, CA19-9, CA15-2, and CA125 were normal. The urinary levels of vanillyl mandelic acid and homovanillic acid were also normal.

Computer-assisted tomography of the abdomen displayed a huge solid mass with speckled calcification, including cystic lesions suggesting neuroblastoma. Chest X-ray revealed no abnormal shadow. Neither bone scan nor gallium scintigraphy showed any metastasis. Exploratory laparotomy on June 16 (dl) revealed a large hypervascular tumor, and a rapid tentative diagnosis of the

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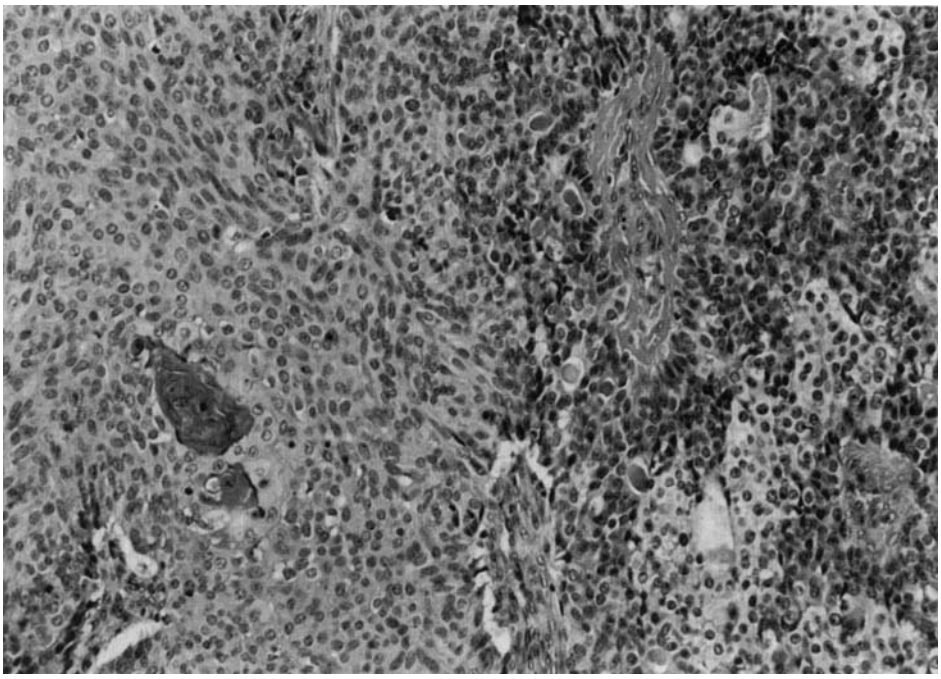

Fig. 1. Tumor microphotography. x400. Stained with hematoxylin and eosin. Note a squamoid corpuscle with keratinization.

biopsy specimen was neuroblastoma. Therefore, chemotherapy was started: cyclophosphamide, 1,000 mg/m^2/d at d5 and d6; vincristine, 1.6 mg/m^2 at d6. However, on June 22 (d7), a definite diagnosis of pancreatoblastoma was obtained. Angiography on June 26 (d11) revealed hypervascularity and suggested a possibility of resection of the tumor. The next day (d12), the patient underwent surgical treatment (distal partial pancreatectomy, pyloroplasty, and splenectomy). The encapsulated hypervascular tumor arose from the body-to-tail of the pancreas and adhered to the stomach and spleen. Because of tumor spillage that occurred during resection, cyclophosphamide (150 mg/m^2 at d12) and adriamycin (35 mg/m^2 at d19) were administered intravenously. Thereafter, a total of 40 Gy (2 Gy $\times$ 20 times over 28 days from d34 to d61) of radiation was given to the epigastrium and paraaorta. The tumor resected weighed 1,260 g and measured 18 $\times$ 11 $\times$ 8 cm. Splenic metastasis was found and measured 3.7 $\times$ 2.3 cm. The tumor consisted of epithelial cells showing tubular and acinar patterns. Squamoid corpuscles surrounded by acinar arrangement of epithelial cells were seen in some areas (Fig. 1).

Immunoperoxidase staining for alpha 1-antitrypsin was positive. Five weeks after removal of the tumor, laboratory examination revealed a return to normal of the serum levels of tissue polypeptide antigen (65 U/l), alpha-fetoprotein (0 ng/ml), neuron specific enolase (10 ng/ml), trypsin (62 ng/ml), and lactate dehydrogenase (199 U).

Metastasis to the right hepatic lobe was found on March 26, 1990, 9 months after resection by computer-assisted tomography. The metastatic tumor protruded from the inferior surface of the liver. And then, periodical laboratory examination revealed slight elevation of serum alpha-fetoprotein (14.6 ng/ml). Partial hepatectomy (S_6) was performed on April 6, 1990. The metastatic tumor was 4 $\times$ 4.5 $\times$ 4.3 cm in size and 55 g in weight. Four days later, the serum alpha-fetoprotein level decreased to 5.0 ng/ml. Subsequently, the patient was treated with a chemotherapy regimen using cisplatin (30 mg/m^2 at d1, 60 mg/m^2 at d9, and 90 mg/m^2 at d16), adriamycin (30 mg/m^2/d from d36 to d38), vincristine (2mg/m^2 at d57), and cyclophosphamide (500 mg/m^2/d at d58 and d59). After completion of the chemotherapy, the patient had a 14-month uneventful postoperative course until the discovery of a locally recurrent tumor by computer-assisted tomography. Then, the serum level of alpha-fetoprotein was noticed to increase to 19.2 ng/ml. Gallium scintigraphy 1 month prior to the computer-assisted tomography showed no abnormal accumulation. On October 15, 1991, he underwent the fourth surgery (extirpation of the recurrent tumor, partial hepatectomy, partial colectomy, and partial gastrectomy) and intraoperative radiation of 20 Gy. He currently shows no evidence of disease at 6 years and 1 month after initial diagnosis.

DISCUSSION

Pancreatoblastoma was first proposed as a disease entity by Horie et al. [4]. Because of the rarity of cases and of confusion of nomenclature due to different interpreta-

TABLE I. Reported Cases of Pancreatoblastoma Received Radiation Therapy and/or Chemotherapy

Case	Author year, reference	Age/ sex	Site	Size (cm)	Treatment[a]	Outcome
1	Tsukimoto et al., 1973 [7]	4/F	Head	10 × 8	EL—Ch (CPA, VCR)—tumor shrinkage	Died 30 days after EL
2	Kakudo et al., 1976 [8]	3/F	Tail	15 × 5 × 5	Re—liver metastasis—Ch—liver tumor shrinkage—local recurrence—Re	Died 2 years after 2nd Re
3	Horie et al., 1977 [4]	4/M	Head	11 × 9 × 8.5	Re—Ir (40 Gy)	Healthy 20 years after Re
4	Mierau and Orsini, 1983 [16]	16/F	Head	—	EL—Ch (5-FU, ADM, MMC)	Died 18 months after diagnosis
5	Buchino et al., 1984 [11]	3/M	Body	11 × 8 × 8.5	Re—Ir (40 Gy)—liver metastasis—Re	NED 12 months after 2nd Re
6	Ohaki et al., 1985 [9]	6/M	Whole	Child head	EL—Ir + Ch—incomplete Re—Ch (5-FU, ADM, MMC, VCR) + Ir (130 Gy)—liver metastasis	Died 3 years after diagnosis
7	Iseki et al., 1986 [17]	8/M	Tail	17 × 9 × 9	Primary tumor: Re—Ch (VCR, ADM, CPA); Bone metastasis: resolved by the Ch	NED 2 years after Re
8	Palosaari et al., 1986 [1]	37/M	Head	8	EL—Ch (5-FU, ADM, MMC): noneffective—intraoperative & external Ir (60 Gy)—tumor shrinkage—liver metastasis	?
9	Griffin et al., 1987 [12]	2/F	Head?	10 × 7 × 6	Re—recurrence—Re—recurrence—Ir (46.2 Gy)—tumor shrinkage	Asymptomatic 2 years after completion of Ir
10	Grosfeld et al., 1990 [13]	4/M	—	—	Re—Ir (30 Gy)—liver metastasis—partial hepatectomy—Ch	NED 6 years after partial hepatectomy
11	Silverman et al., 1990 [14]	4/M	—	—	Re—Ir (40 Gy)—Ch (CDDP, VP16)	NED 7 months after Re
12	Vannier et al., 1991 [15]	3/M	Body and tail	9 × 5.5 × 6.5	EL—Ch (IFM, VCR, ACT): noneffective—Ch (CDDP, ADM)—tumor shrinkage—Re—Ir (70 Gy)	NED 40 months after completion of treatment
13	Vannier et al., 1991 [15]	6/F	Head	7.5 × 5	EL—Ch (CPA, ACT, BLM, VBL, CDDP)—tumor shrinkage—regional relapse (LN)—Ch (IFM, VP16, EPI-ADM, VCR)—Ir (36 Gy)—2nd remission—2nd relapse (supraclavicular LN and liver)—the same Ch as the initial Ch	Died 36 months after diagnosis
14	Inomata et al., 1992 [18]	5/F	Tail	8 × 7 × 7	EL—Ch (THP-ADM, CDDP)—tumor shrinkage—Re—Ch (CDDP, THP-ADM, CPA, ACT, VCR)	NED 16 months after Re
15	Chung et al., 1992 [19]	3/F	Body	6 × 5 × 5	Re—liver metastasis—Ch	To be poor
16	Present case	5/M	Body and tail	18 × 11 × 8	EL—Ch (CPA, VCR)—Re—Ch (CPA, ADM)—Ir (40 Gy)—liver metastasis—partial hepatectomy—Ch (CDDP, ADM, VCR, CPA)—local recurrence—radical surgery + intraoperative Ir (40 Gy)	NED 3 years 8 months after 4th surgery

[a]Abbreviations: EL, exploratory laparotomy; Ch, chemotherapy; Ir, radiation therapy; Re, resection; NED, no evidence of disease; CPA, cyclophosphamide; VCR, vincristine; 5-FU, 5-fluorouracil; ADM, adriamycin (doxorubicin); MMC, mitomycin C; CDDP, cisplatin; VP16, etoposide; IFM, ifosfamide; ACT, actinomycin D; BLM, bleomycin; VBL, vinblastin; EPI-ADM, epirubicin; LN, lymphnode.

tion for the histopathological specimens [4–6], some different tumors might have been erroneously diagnosed as pancreatoblastoma. Conversely, the patients of Tsukimoto et al. [7], Kakudo et al. [8], Ohaki et al. [9], and Ichijima et al. [10] were later diagnosed as pancreatoblastoma by Horie [5]. Each of these lesions was called initially adenocarcinoma [7], solid-type adenocarcinoma with acinar and cordlike pattern [8], well-differentiated adenocarcinoma with distinct ductal and acinar differentiation in autopsy material [9], and acinar cell carcinoma with endocrine component [10], respectively, although the initial and second biopsy specimens were consistent with pancreatoblastoma in the patient of Ohaki et al. [9].

Pancreatoblastoma behaves like a benign tumor, and complete removal of the tumor would warrant a favorable prognosis. However, tumor spillage occurred during re-

section in our patient. A combination of postoperative radiation therapy (40 Gy) and chemotherapy with cyclophosphamide and adriamycin failed to prevent liver metastasis. Moreover, a more intensive chemotherapy regimen using cicplatin, adriamycin, vincristine, and cyclophosphamide that was given after partial hepatectomy, failed to prevent the tumor from locally recurring. We were thus confronted with therapeutic difficulties when tumor spillage occurred during resection as well as when the tumor was unresectable at diagnosis. The long-term outcome of such cases appears never to be favorable.

Description of radiation therapy could be found in nine patients [1,4,9,11–15], to our knowledge, in the literature, six of whom also received chemotherapy [1,9,13–15] (Table I). The case of Griffin et al. [12] is noteworthy. A locally recurrent tumor was successfully treated by radiation alone; exploratory laparotomy 6 weeks after completion of radiotherapy showed no evidence of tumor by multiple biopsies. In the case of Palosaari et al. [1], an unresectable primary tumor had no response to chemotherapy, but radiation therapy resulted in substantial tumor shrinkage. Thus in some cases radiation therapy will bring a decrease in size or regression of locally recurrent tumors as well as primary tumors. Another two patients who received postoperative radiation therapy had no local recurrence in spite of liver metastasis [11,13], which suggests a preventive effect of postoperative radiation therapy on local recurrence.

We identified 12 patients in the literature who had been treated with chemotherapy [1, 7–9, 13–19] (Table I). In three of the 12 patients, chemotherapy had no apparent effect on a primary tumor [1, 16] or metastatic tumor [19], in two of whom 5-fluorouracil, adriamycin, and mitomycin C were used. On the contrary, another six patients showed a decrease in size of tumor, primary [7,9,15,18] or metastatic [8]. The patient of Tsukimoto et al. [7] was treated with weekly intravenous administration of cyclophosphamide and vincristine on alternate weeks. The primary tumor mass decreased markedly in size within 10 days, but the patient became comatose on the 30th day and died.

A decrease in size of tumor by chemotherapy permitted resection of the primary tumor in the case of Vannier et al. [15] using cisplatin and adriamycin, and in Inomata et al.'s case [18] using THP-adriamycin and cisplatin although in the former, a chemotherapy regimen using ifosfamide, vincristine, and actinomycin D was not effective. An interesting case has been reported by Iseki et al. [17], in which distant metastasis to the distal right radius was resolved by chemotherapy using vincristine, adriamycin, and cyclophosphamide, although such distant metastasis is rare in pancreatoblastoma [20]. Evaluation of each of these chemotherapeutic agents is difficult because of the rarity of cases. A long-term effect of chemotherapy appears to be questionable. Indeed, the long-term outcome depends on complete removal of tumor, whether primary, metastatic, or locally recurrent. Therefore, complete tumor resection should follow the tumor shrinkage by chemotherapy, if feasible.

Our patient showed an increase in serum alpha-fetoprotein at diagnosis and its return to normal after tumor resection. Thus elevated serum alpha-fetoprotein levels are found in approximately half of patients with pancreatoblastoma [9,11,15,17,18,21]. There is a report that serum alpha-fetoprotein can be a good marker in the course [9]. In the patient reported by Iseki et al. [17], however, the serum level returned to normal after removal of the primary tumor in spite of an existing metastatic tumor. In another two patients [15,18], the serum alpha-fetoprotein level also returned to normal after chemotherapy in spite of the demonstration of residual tumor tissue. In our patient, the serum levels had been normal until the discovery of liver metastasis or local recurrence by computer-assisted tomography. These indicate that elevation of serum alpha-fetoprotein levels necessitates a considerable tumor mass, even if it were an alpha-fetoprotein-producing tumor. In addition, a previous immunohistochemical study could not demonstrate alpha-fetoprotein in the tumor cells in a specimen in spite of the elevation of serum alpha-fetoprotein [5]. In such a case, liver metastasis may be responsible for the elevation of serum alpha-fetoprotein and paraneoplastic hepatic cells may produce alpha-fetoprotein [22]. Therefore, serum alpha-fetoprotein is not necessarily a good marker in the course.

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